

Patent Application
Attorney Docket No. *PC11861A*

I hereby certify that this correspondence is being deposited with the United States Postal Service as first-class mail in an envelope addressed to Hon. Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 on this 30 day of September, 2003.

By

Janice Denison
(Signature of person mailing)
Janice Denison

(Typed or printed name of person)

RECEIVED

OCT 15 2003

TC 1700

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Frank Lombardo, et al. :

APPLICATION NO.: 10/081,784 : Examiner: To be assigned

FILING DATE: 02/21/2002 : Group Art Unit: 2857

TITLE: TOOL FOR LIPOPHILICITY :
DETERMINATION IN DRUG DISCOVERY
BASIC AND NEUTRAL COMPOUNDS

Hon. Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Sir:

INFORMATION DISCLOSURE STATEMENT
PURSUANT TO 37 C.F.R. § 1.97 ET SEQ and § 1.98

Pursuant to 37 CFR § 1.97 Applicants herein make available to the U.S. Patent and Trademark Office a copy of PTO-FB-A820 which lists the references cited by the Applicants, copies of which are enclosed. Applicants cite a total of 68 references, four of which are non-English language documents.

Examiner is requested to consider carefully the complete text of the 64 English language references in connection with the examination of the above-identified Application in accord with 37 C.F.R. § 1.104(a).

With respect to the four non-English language documents, since Applicants do not have in their possession, custody or control a written English translation, Applicants have herein provided in accordance with MPEP §609 III A(2) and (3) a concise explanation of the non-English document's relevance, as it is presently understood by the Applicants.

(1) Büchi, V., et al., *Zusammenhänge zwischen der chemischen Konstitution, den physikalisch-chemischen Eigenschaften, der chemischen reaktivität und der lokalanästhetischen Wirksamkeit einiger Procain-Isostere*, Arzneim.-Forsch., Vol. 22: 1071-

1084, 1972. Page 1080 Table 3.4 of the reference cites the “Verteilungsloeffizienten” or “partition coefficient” of compound Procainamide. Applicants utilized this data to calculate the average logD_{oct} of said compound, as disclosed in Table 1 page 12 of the Application as originally filed.

(2) Graf, E., et al., *pK- und V_k-Messungen an Benzodiazepinen*, Pharm. Uns. Zeit., Vol. 6: 171-178, 1977. Page 178, lines 4-5 of the reference cites the “Verteilungsloeffizienten” or “partition coefficient” of the compound Lormetazepam. Applicants utilized this data to calculate the average logD_{oct} of said compound, as disclosed in Table 1 page 11 of the Application as originally filed.

(3) Mohler, V., et al., *On Chemistry and synthesis of 3,7-dimethyl-1-(5-oxo-hexyl)-xanthine*, Arzneim.-Forsch., Vol. 21: 1159-1160, 1971. Page 1159 of the reference cites the “Verteilungsloeffizienten” or “partition coefficient” of “BL 191” or the compound Pentoxifylline. Applicants utilized this data to calculate the average logD_{oct} of said compound, as disclosed in Table 1 page 11 of the Application as originally filed.

(4) Schutz, V., et al., *Screening, detection and biotransformation of Lormetazepam, a new hypnotic agent from the 1,4-benzodiazepine series*, Arzneim.-Forsch., Vol. 32: 177-183, 1977. Table 5 on page 178 of reference cites the “Verteilungsloeffizienten” or “partition coefficient” of the compound Lorazepam. Applicants utilized this data to calculate the average logD_{oct} of said compound, as disclosed in Table 1 page 11 of the Application as originally filed.

Examiner is requested to consider the above text taken from the non-English references in connection with the examination of the above-identified Application in accord with 37 C.F.R. § 1.104(a).

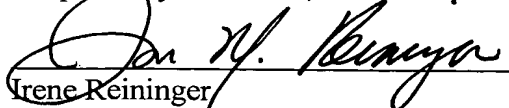
It is believed the Examiner will concur with Applicants’ belief that the subject matter presently claimed is neither anticipated nor rendered obvious by the foregoing references.

It is requested that the references listed on the attached form PTO-FB-A820 be included in the “References Cited” portion of any patent issuing from this application (M.P.E.P. § 1302.12).

A prompt and favorable response is earnestly solicited.

Date: September 30, 2003

Respectfully submitted,


Irene Reininger
Attorney for Applicants
Reg. No. 48,439

Pfizer Inc.
Patent Department, MS 8260-1611
Eastern Point Road
Groton, Connecticut 06340
(860) 715-5756

Date Mailed: 09/30/2003 Express Mail No.

Application No. 10/081,784 Docket No. PC11861A By JDM

Application of Frank Lombardo, et al.

Entitled TOOL FOR LIPOPHILICITY DETERMINATION IN DRUG DISCOVERY BASIC
AND NEUTRAL COMPOUNDS

The following, due in the U.S. Patent and Trademark Office, has been received there
on the date stamped hereon:

<input type="checkbox"/> Specification _____ pages	<input type="checkbox"/> Amendment
<input type="checkbox"/> Claims _____ pages	<input type="checkbox"/> Reply
<input type="checkbox"/> Abstract _____ pages	<input type="checkbox"/> Notice of Appeal
<input type="checkbox"/> Drawing(s) _____ sheets	<input type="checkbox"/> Brief (3 copies)
<input type="checkbox"/> Declaration with <input type="checkbox"/> Power of Attorney	<input type="checkbox"/> Petition for Extension of Time
<input type="checkbox"/> Assignment & Recordation Cover Sheet	<input type="checkbox"/> Filing of Missing Parts
<input type="checkbox"/> Letter of Transmittal	<input type="checkbox"/> Express Mail Certificate
<input checked="" type="checkbox"/> Disclosure Statement 68 References	<input type="checkbox"/> Associate Power of Attorney
<input checked="" type="checkbox"/> Form PTO-FB-A620	<input type="checkbox"/> Petition for Expedited Issuance for Foreign Filing License
<input type="checkbox"/> Issue Fee Transmittal	<input type="checkbox"/> Provisional Cover Sheet
<input type="checkbox"/> Fee Address Indication Form	<input type="checkbox"/> PTO-1390 (DO/EO/US) _____ pages
<input type="checkbox"/> Priority Document	<input type="checkbox"/> Form PTO-1050
<input type="checkbox"/> Cert. of Correction under 37 CFR 1.322(a)	
<input type="checkbox"/>	
<input type="checkbox"/>	

INFORMATION DISCLOSURE CITATION (Use separate sheets if necessary)				ATTY. DOCKET NO. PC11861A				SERIAL NO. 10/081,784				
APPLICANT Frank Lombardo, et al.				FILING DATE 02/21/2002				GROUP 2857				
U.S. PATENT DOCUMENTS												
EXAMINER INITIAL				DOCUMENT NUMBER			DATE		NAME		FILING DATE IF APPROPRIATE	
FOREIGN PATENT DOCUMENTS												
				DOCUMENT NUMBER			DATE	COUNTRY		CLASS	SUBCLASS	TRANSLATION
												YES NO
OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)												
			Abraham, M., et al., <i>Hydrogen bonding XXXV. Relationship between high-performance liquid chromatography capacity factors and water-octanol partition coefficients</i> , <u>J. Chromatogr.</u> , Vol. 685: 203-211, 1994									
			Adams, G., et al., <i>Structure-activity relationships in the development of hypoxic cell radiosensitizers</i> , <u>Int. J. Radiat. Biol.</u> , Vol. 35 (2): 133-150, 1979									
			Alessi-Severini, S., et al., <i>Flecainide</i> , In <u>Analytical profiles of drug substances and excipients</u> , Vol. 21: 169-195, 1992									
			Anderson, B., et al., <i>Effects of lipophilicity of nitroimidazoles on radiosensitization of hypoxic bacterial cells in vitro</i> , <u>Br. J. Cancer</u> , Vol. 39: 705-710, 1979									
			Artursson, P., et al., <i>Correlation between oral drug absorption in humans and apparent drug permeability coefficients in human intestinal epithelia (CACO-2) cells</i> , <u>Biochem. Biophys. Res. Comm.</u> , Vol. 175(3): 880-885, 1991									
			Avdeef, A., <i>Assessment of distribution-pH profiles</i> , <u>Lipophilicity in drug action and toxicology</u> , CH. 7: 110-139, 1996									
			Barbato, F., et al., <i>Hydrophobic constants and quantitative structure activity relationships (QSAR) in sets of phenothiazine drugs</i> , <u>Eur. J. Med. Chem. - Chim. Ther.</u> , Vol. 17(3): 229-234, 1982									
			Barbato, F., et al., <i>Chromatographic indices determined on an immobilized artificial membrane (IAM) column as descriptors of lipophilic and polar interactions of 4-phnyldihydropyridine calcium-channel blockers with biomembranes</i> , <u>Eur. J. Med. Chem.</u> , Vol. 31: 311-318, 1996									
			Barbato, F., et al., <i>Relationships between octanol-water partition dat, chromatographic indices and their dependence on pH in a set of beta-adrenoceptor blocking agents</i> , <u>Il Farmaco</u> , Vol. 45(6): 647-663, 1990									
			Berthod, A., et al., <i>Hydrophobicity of ionizable compounds. A theoretical study and measurements of diuretic octanol-water partition coefficients by countercurrent chromatography</i> , <u>Anal. Chem.</u> , Vol. 71: 879-888, 1999									
			Büchi, V., et al., <i>Zusammenhänge zwischen der chemischen Konstitution, den physikalisch-chemischen Eigenschaften, der chemischen reaktivität und der lokalanästhetischen Wirksamkeit einiger Procain-Isostere</i> , <u>Arzneim.-Forsch.</u> , Vol. 22: 1071-1084, 1972									
			Bundgaard, H., et al., <i>Allopurinol prodrugs. II. Synthesis, hydrolysis kinetics and physicochemical properties of various N-acyloxymethyl allopurinol derivatives</i> , <u>Inter. J. Pharm.</u> , Vol. 24: 307-325, 1985									
			Camenisch, G., et al., <i>Estimation of permeability by passive diffusion through Caco-2 cell monolayers using the drugs' lipophilicity and molecular weight</i> , <u>Eur. J. Pharm. Sci.</u> , Vol. 6:313-319, 1998									
			Carelli, V., et al., <i>Enhancement effects in the permeation of Alprazolam through hairless mouse skin</i> , <u>Inter. J. Pharm.</u> , Vol. 88: 89-97, 1992									
EXAMINER			DATE CONSIDERED			RECEIVED OCT 14 2003 TC 1700						

INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)				ATTY. DOCKET NO. PC11861A				SERIAL NO. 10/081,784			
				APPLICANT Frank Lombardo, et al.							
				FILING DATE 02/21/2002				GROUP 2857			

U.S. PATENT DOCUMENTS											
EXAMINER INITIAL	DOCUMENT NUMBER						DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS											
DOCUMENT NUMBER						DATE	COUNTRY	SUBCLASS	TRANSLATION		
									YES NO		

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)											
			Carmichael, F., et al., <i>In Vitro inhibitory effects of narcotic analgesics and other psychotropic drugs on the active uptake of norepinephrine in mouse brain tissue</i> , J. Pharmacol. Exp. Ther., Vol. 186(2): 253-260, 1973								
			Fujita, T., et al., <i>A new substituent constant, π, derived from partition coefficients</i> , J. Am. Chem. Soc., Vol. 86: 5175-5180, 1965								
			Graf, E., et al., <i>pK- und V_k-Messungen an Benzodiazepinen</i> , Pharm. Uns. Zeit., Vol. 6: 171-178, 1977								
			Hansch, E., et al., <i>Structure-Activity relationship of chloramphenicols</i> , J. Med. Chem., Vol. 16(8): 917-922, 1973								
			Hansch, E., et al., <i>Exploring QSAR. Hydrophobic, Electronic, and Steric Constants</i> , American Chemical Society: Washington, D.C., 3-216, 1995								
			Henczi, M., et al., <i>Determination of octanol-water partition coefficients by an HPLC method for anticonvulsant structure-activity studies</i> , J. Pharm. Pharmacol., Vol. 47: 345-347, 1995								
			Iwasa, J., et al., <i>Substituent constants for aliphatic functions obtained from partition coefficients</i> , J. Med. Chem., Vol. 8: 150-153, 1965								
			Jezequel, S., <i>Fluconazole: Interspecies scaling and allometric relationships of pharmacokinetic properties</i> , J. Pharm. Pharmacol., Vol. 46: 196-199, 1994								
			Kaufman, J., et al., <i>Microelectrometric titration measurement of the pK_a's and partition and drug distribution coefficients of narcotics and narcotic antagonists and their pH and temperature dependence</i> , J. Med. Chem., Vol. 18(7): 647-655, 1975								
			Lacko, L., et al., <i>The affinities of Benzodiazepines to the transport protein of glucose in human erythrocytes</i> , Arzneim.-Forsch/Drug Res., Vol. 34(1): 403-407, 1984								
			La Rotonda, et al., <i>Relationships between octanol-water partition data, chromatographic indices and their dependence on pH in a set of nonsteroidal anti-inflammatory drugs</i> , Quant. Struct.-Act. Relat., Vol. 2: 168-173, 1983								
			Lipinski, C., et al., <i>Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings</i> , Advanced Drug Delivery Reviews, Vol. 23: 3-25, 1997								
			Lombardo, F., et al., <i>ElogP_{oct}: A tool for lipophilicity determination in drug discovery</i> , J. Med. Chem., Vol. 43(15): 2922-2928, 2000								

EXAMINER	DATE CONSIDERED
----------	-----------------

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)				ATTY. DOCKET NO. PC11861A				SERIAL NO. 10/081,784			
APPLICANT Frank Lombardo, et al.				FILING DATE 02/21/2002				GROUP 2857			

OCT 02 2003
 U.S. PATENT & TRADEMARK OFFICE

U.S. PATENT DOCUMENTS											
EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE					

FOREIGN PATENT DOCUMENTS												
DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION							
						YES	NO					

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)											
			Lombardo, F., et al., <i>ElogD_{oct}: A tool for lipophilicity determination in drug discovery. 2. Basic and neutral compounds</i> , <u>J. Med. Chem.</u> , Vol. 44(15): 2490-2497, 2001								
			Lüllmann, H., et al., <i>The binding of drugs to different polar lipids in vitro</i> , <u>Biochem. Pharmacol.</u> , Vol. 28: 3409-3415, 1979								
			Maillard, C., et al., <i>Design, synthesis, and pharmacological evaluation of conformationally constrained analogues of N,N-diaryl- and N-Aryl-N-alkylguanidines as potent inhibitors of neuronal Na⁺ channels</i> , <u>J. Med. Chem.</u> , Vol. 41, 3048-3061, 1998								
			Manners, C., et al., <i>Lipophilicity of zwitterionic sulphate conjugates of tiaramide, propranolol and 4'-hydroxypropranolol</i> , <u>Xenobiotica</u> , Vol. 19(12): 1387-1397, 1989								
			Melander, W., et al., <i>Stationary phase effects in reversed-phase chromatography I. Comparison of energetics of retention on alkyl-silica bonded phases</i> , <u>J. Chromatogr.</u> , Vol. 199: 35-56, 1980								
			Meuldermans, W., <i>Plasma protein binding and distribution of fentanyl, sufentanil, alfentanil and lofentanil in blood</i> , <u>Arch. Int. Pharmacodyn.</u> , Vol. 257: 4-19, 1982								
			Minick, D., et al., <i>Modeling octanol-water partition coefficients by reversed-phase liquid chromatography</i> , <u>J. Chromatogr.</u> , Vol. 461: 177-191, 1989								
			Minick, D., et al., <i>A comprehensive method for determining hydrophobicity constants by reversed-phase high-performance liquid chromatography</i> , <u>J. Med. Chem.</u> , Vol. 31: 1923-1933, 1988								
			Mohler, V., et al., <i>On Chemistry and synthesis of 3,7-dimethyl-1-(5-oxo-hexyl)-xanthine</i> , <u>Arzneim.-Forsch.</u> , Vol. 21: 1159-1160, 1971								
			Morelock, M., et al., <i>Estimation and correlation of drug water solubility with pharmacological parameters required for biological activity</i> , <u>J. of Pharm. Sci.</u> , Vol. 83(7): 948-952, 1994								
			Müller, W., et al., <i>Interactions of benzodiazepines with human serum albumin, Circular Dichroism Study</i> , <u>Arch. Pharmacol.</u> , Vol. 278: 301-312, 1973								
			O'Connor, D., et al., <i>Influence of physicochemistry on the brain penetration of the 'triptans in rat</i> , <u>Poster presented at the XIV Course in Drug Research</u> , Helsinki, Finland, June 5-6, 1997								

EXAMINER	DATE CONSIDERED
EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)				ATTY. DOCKET NO. PC11861A				SERIAL NO. 10/081,784				
				APPLICANT Frank Lombardo, et al.								
				FILING DATE 02/21/2002				GROUP 2857				
U.S. PATENT DOCUMENTS												
EXAMINER INITIAL	DOCUMENT NUMBER							DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
FOREIGN PATENT DOCUMENTS												
DOCUMENT NUMBER								DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES NO
OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)												
			Okada, J., et al., ¹³ C nuclear magnetic resonance spectra of antipyrine derivatives and their application to hansch analysis, <u>Chem. Pharm. Bull.</u> , Vol. 24(1): 61-71, 1976									
			Pagliara, A., et al., Structural properties governing retention mechanisms on RP-HPLC stationary phases used for lipophilicity measurements, <u>Journal of Liquid Chromatography</u> , Vol. 18(9): 1721-1745, 1995									
			Pauletti, G., et al., Can counterions affect the transport of a lipophilic diarylguanidine (CNS 1237) across caco-2 cell monolayers in vitro?, <u>Pharm. Res.</u> , Vol. 14: S-24, 1997									
			Perlman, M., et al., Use of pH dependence of log D for PKA determination and formulation of diarylguanidines, <u>Pharm. Res.</u> , Vol. 13: S-339, 1996									
			Prierew, H., et al., Solubility and distribution coefficient of potassium and magnesium retaining triamterene derivatives, <u>Pharmazie</u> , Vol. 51: 279-282, 1996									
			Sangster, J., <u>Octanol-water partition coefficients: Fundamentals and Physical Chemistry</u> , Wiley, New York, 79-112, 1997									
			Scherrer, R., et al., Use of distribution coefficients in quantitative structure-activity relationships, <u>J. Med. Chem.</u> , Vol. 20(1): 53-58, 1977									
			Schutz, V., et al., Screening, detection and biotransformation of Lormetazepam, a new hypnotic agent from the 1,4-benzodiazepine series, <u>Arzneim.-Forsch.</u> , Vol. 32: 177-183, 1977									
			Seiler, P., et al., 5-Phenyl-1,3-dihydro-1,4-benzodiazepin-2-ones, Experimental verification of substituent constants, <u>Arzneim.-Forsch./Drug Res.</u> , Vol. 33: 1519-1522, 1983									
			Sirius Technical Application Notes, Sirius Analytical Instruments, Ltd., Forest Row, East Sussex RH18 5DW, Vol. 1: pages 2, 3, 8, 84, 85, 86, 99b, 99c, 122 & 123, 1994									
			Sirius Technical Application Notes, Sirius Analytical Instruments, Ltd., Forest Row, East Sussex RH18 5DW, Vol. 2: pages 36, 37, 81, 82, 83, 84, 114, 115, 167 & 168, 1995									
			Slater, B., et al., pH-metric log P. 4. Comparison of partition coefficients determined by HPLC and potentiometric methods to literature values, <u>J. Pharm. Sci.</u> , Vol. 83(9): 1280-1283, 1994									
			Smith, D., et al., Physicochemical properties in drug metabolism and pharmacokinetics, <u>Computer-Assisted Lead Finding and Optimization</u> , Ch. 17: 265-276, 1997									
EXAMINER				DATE CONSIDERED								
EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.												

RECEIVED

OCT 16 2003

TC 1700

INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)				ATTY. DOCKET NO. PC11861A				SERIAL NO. 10/081,784				
				APPLICANT Frank Lombardo, et al.								
				FILING DATE 02/21/2002				GROUP 2857				
U.S. PATENT DOCUMENTS												
EXAMINER INITIAL	DOCUMENT NUMBER							DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
FOREIGN PATENT DOCUMENTS												
DOCUMENT NUMBER							DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
											YES	NO
OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)												
			Smith, D., et al., <i>Design of drugs involving the concepts and theories of drug metabolism and pharmacokinetics</i> , <u>Medicinal Research Reviews</u> , Vol. 16(3): 243-266, 1996									
			Stopher, D., et al., <i>An improved method for the determination of distribution coefficients</i> , <u>J. Pharm. Pharmacol.</u> , Vol. 42: 144, 1989									
			Taylor, P., <i>Hydrophobic properties of drugs</i> , In <u>Comprehensive Medicinal Chemistry</u> , Vol. 5: 241-294, 1990									
			ter Laak, A., et al., <i>Lipophilicity and hydrogen-bonding capacity of H₁-antihistaminic agents in relation to their central sedative side-effects</i> , <u>Eur. J. Pharm. Sci.</u> , Vol. 2: 373-384, 1994									
			Timmermans, P., et al., <i>Lipophilicity and brain disposition of clonidine and structurally related imidazolidines</i> , <u>Naunyn-Schmiedeberg's Arch. Pharmacol.</u> , Vol. 300: 217-226, 1977									
			Tomida, H., et al., <i>Solubilization of steroid hormones by polyxyethylene lauryl ether</i> , <u>Chem. Pharm. Bull.</u> , Vol. 26(9): 2832-2837, 1978									
			Tsai, R., et al., <i>Influences of stereochemical factors on the partition coefficient of diastereomers in a biphasic octan-1-ol/water system</i> , <u>J. Chem. Res. (M)</u> : 1901-1920, 1993									
			Ungell, A., et al., <i>Membrane transport of drugs in different regions of the intestinal tract of the rat</i> , <u>J. Pharm. Sci.</u> , Vol. 87(3): 360-366, 1998									
			Unger, S., et al., <i>Octanol-physiological buffer distribution coefficients of lipophilic amines by reversed-phase high-performance liquid chromatography and their correlation with biological activity</i> , <u>J. Med. Chem.</u> , Vol. 24: 262-270, 1981									
			Valko, K., et al., <i>Chromatographic hydrophobicity index by fast-gradient RP-HPLC: A high-throughput alternative to log P/log D</i> , <u>Analytical Chemistry</u> , Vol. 69(11): 2022-2029, 1997									
			Van de Waterbeemd, H. et al., <i>Lipophilicity measurements by reversed-phase high performance liquid chromatography (RP-HPLC)</i> , <u>Lipophilicity in Drug Action and Toxicology</u> , Ch. 5: 73-87, 1996									
			Winiwarter, S., et al., <i>Correlation of human jejunal permeability (in vivo) of drugs with experimentally and theoretically derived parameters. A multivariate data analysis approach</i> , <u>J. Med. Chem.</u> , Vol. 41: 4939-4949, 1998									
EXAMINER				DATE CONSIDERED								
EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.												

